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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,278	03/12/2004	Hiroyuki Araki	250193US0CONT	6451

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,278	ARAKI ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 4-8* is/are pending in the application.

4a) Of the above claim(s) *5-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/971,611.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-12-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 4, 5-8 are currently pending and are present for examination. Claims 2, 4, and 8 are now under consideration. Claims 5-7 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 2, 4 and 8 in paper filed on 10-25-06 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups I-II would not pose an undue burden on the Examiner. Applicant argues that restriction is only proper if the claims of the restricted groups are independent or patentably distinct and there would be a serious burden placed on the Examiner if restriction is not required (M.P.E.P. § 803) and that the burden of proof is on the Examiner to provide reasons and/or examples to support any conclusion in regard to patentable distinction (M.P.E.P. § 803). According to applicant the claims of Group I are integrally linked with the claims of Group II and that the claims of Group II (a gene encoding a mutant a-amylase) are critical to making the mutant or-amylase of Group I and therefore the claims of Groups I and II are interdependent and should be examined together. Examiner respectfully disagrees. Examiner has clearly explained as to how the inventions of the two groups are unrelated and are structurally and functionally distinct from each other in the previous Office action. Examiner also reminds applicants that restriction is not based on whether inventions are "integrally linked with each other" but based on structure and function of the products claimed. In the instant case arguing that the gene of group II which is a product, that is structurally and functionally different from the encoded polypeptide of group I is

interdependent and integrally linked and therefore restriction must be withdrawn is a highly misplaced argument. As stated earlier the two inventions are distinct from each other and are classified in different classes and subclass.

Applicant also argues that there is a commonality that exists between Group I and Group II and it is a technical relationship that involves common features that define the contribution which each of the groups taken as a whole makes over the prior art. Examiner respectfully disagrees with such a line of argument. Applicant is applying an interpretation of restriction rules that is normally used to restrict a PCT 371 National Stage application to a US non-provisional application. Such a line of argument is again highly misplaced and flawed.

Applicant also argues that the Examiner simply alleges that the claims of Group I are unrelated to the claims of Group II and do not require each other for practice and that the Examiner has failed to supply any references or specific examples to support the allegation of separate invention, and the Office has failed to show that a burden exists in searching all of the claims. Examiner respectfully disagrees. Examiner is at a loss to understand the argument of applicant in which he argues that examiner has not provided any references and specific examples. It is not clear to the Examiner as to what more can be done to show the common knowledge, or basic high school level knowledge, that a polynucleotide and polypeptide are structurally and functionally different from each other, classified in different classes and subclasses, that polynucleotides are polymers of "nucleotides" whereas polypeptides are polymers of "amino acids" and therefore these are different and distinct inventions. If the applicant needs any more explanation as to how polynucleotides and polypeptides are different

from each other and why they are considered as two different inventions, Examiner suggests the book "Biochemistry" by Lubert Stryer, WH Freeman and Co., NY, 1989.

Applicant also argues that restriction is only proper if the claims of the restricted groups are not related and that the M.P.E.P. § 803 states as follows:

> If search and examination of an entire application can be made without a serious burden, the Examiner must examine it on its merits even though it includes claims to distinct and independent inventions.

Applicant submits that a search of all the claims would not constitute a serious burden on the Office. Examiner disagrees. Contrary to applicant's argument, searching of the two groups does place an undue burden on the Examiner. The polynucleotides are searched on separate databases and polypeptide seqeucnes are searched on separate databases. The search for the two inventions are not co-extensive. The search for Groups I and II would each require the search of subclasses unnecessary for the search of elected Group I. Furthermore, searching of these databases not only involves just "searching" but also analyzing the enormous search results. The search also involves not just patent databases but also several non-patent literature databases.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 13.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/971611, filed on 10-9-01.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application that has matured in to a US patent. Examiner urges applicants to amend said information by providing the US patent number in response to this Office action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2 and 4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 2 and 4 are drawn to a mutant α-amylase derived from SEQ ID NO:4. While it appears that applicant has indeed derived the mutant enzyme from SEQ ID NO:4, the claim as written reads on a natural mutant found in nature that is also naturally derived from SEQ ID NO:4. Therefore, claims could read on a product of nature. Examiner

suggests amending the claim to recite "an isolated" to show the hand of man which also overcomes this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the position 181 in SEQ D NO:4 as the amino acid "Gln". However, a perusal of the SEQ ID NO:4 shows that the amino acid at that position is Asn. Therefore it is not clear as to which position or which amino acid change is being claimed. Correction is required.

Claims 2, 4, 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 is drawn to a mutant enzyme derived from SEQ ID NO:4. However, not all mutant enzymes continue to have their original activity. Therefore it is not clear whether the said mutant continues to function as amylase. Examiner requests clarification. Examiner also suggests amending the claim to recite "wherein said mutant continues to function as an amylase".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant amylase wherein amino acids in at least one of the following corresponding positions, 128, 140, 144, 168, 181, 272, 375, 466 in SEQ ID NO:4 are substituted or deleted and wherein said polypeptide continues to have the amylolytic activity, does not reasonably provide enablement for any such mutant derived from an amino acid sequence that is at least 60% identical to SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 2, 4, 8 are so broad as to encompass mutants of any or all amylases having 60% identity to the enzyme of SEQ ID NO:4. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of amylases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and

guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of a single amylase with SEQ ID NO:4. It would require undue experimentation of the skilled artisan to make the polypeptide sequence that is 60% identical to SEQ ID NO:4 and use the same to make mutant enzymes. The specification is limited to teaching the use of SEQ ID NO:4 as the amylase but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to

modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass mutants of any or all amylases with 60% identity to the enzyme of SEQ ID NOS:4 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting amylase activity; (B) the general tolerance of amylases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including amylases with an enormous number of amino acid modifications in SEQ ID NO:4. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of amylase mutants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

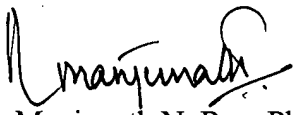
Claims 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsukamoto et al. (GenBank accession No. P19571, 1991) and / or Igarashi et al. (GenBank Acc No. O82839, 1998). This rejection is based upon the public availability of printed publication. Claims 2 and 4 of the instant application are drawn to variant amylase wherein amino acids in at least one of the following corresponding positions, 128, 140, 144, 168, 181, 272, 375, 466 in SEQ ID NO:4 are substituted or deleted (claim 2) and the substitution is substitution of Ser in positions 144 and 375 with Pro. Tsukamoto et al. and Igarashi et al. disclose such a mutant in which the amino acids in all the above stipulated positions except for 168, 207 and 434 are substituted and wherein the amino acid Ser in positions 144 and 375 is substituted with a proline.
Thus Tsukamoto et al. and Igarashi et al. anticipate claims 2 and 4 of this application as written.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

January 11, 2007